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PATREA L. PABST
PABST PATENT GROUP LLP
400 COLONY SQUARE
SUITE 1200
ATLANTA, GA 30361

EXAMINER

DIBRINO, MARIANNE NMN

ART UNIT PAPER NUMBER

1644

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/003,983

Applicant(s)

STAUSS ET AL.

Examiner

DiBrino Marianne

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 7/23/02, 2/2/05, 1/16/04, 11/8/02, 9/13/02 and 7/23/02.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-41 is/are pending in the application.
- 4a) Of the above claim(s) 5 and 8-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6 and 7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4/25/02</u> | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Applicant's amendment filed 7/23/02 and Applicant's responses filed 2/2/05, 1/16/04, 11/8/02, 9/13/02 and 7/23/02 are acknowledged and have been entered.
2. Applicant's election with traverse of Group I (claims 1-7), and species of SEQ ID NO: 1 containing peptide bonds in Applicant's response filed 2/2/05 is acknowledged.

The basis for the traversal is of record in Applicant's said response on pages 4-7.

Applicant's arguments have been fully considered but are not persuasive.

There are two criteria for a proper requirement for restriction between patentably distinct inventions:

(1) The inventions must be independent (see MPEP, 802.01, 806.04, 808.01) **or** distinct as claimed (see MPEP, 806.05 - 806.05(I)); and

(2) There must be a serious burden on the Examiner if restriction is not required (see MPEP, 803.02, 806.04(a) - (j), 808.01(a) and 808.02). Regarding undue burden, the M.P.E.P., 803 (July 1998) states that: For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search.

The restriction requirement enunciated in the previous Office Action meets this criterion of serious burden and therefore establishes that serious burden is placed on the Examiner by the examination of additional Groups, and the inventions are distinct for reasons elaborated in paragraphs 1-9 of the previous Office Action. Thus the said restriction requirement meets the criteria that the inventions are distinct and that there is serious burden. With further regard to Applicant's arguments pertaining to elected Group I, the peptides of Group I (claims 1-7) have a different classification than the library of Group XIII (claim 40) indicating serious burden, and the library of Group XIII is distinct from the peptide of Invention I because the library is a composition of many different individual peptides that bind to many different HLA molecules and elicit differently restricted T cell immune reactions, indicating that the inventions are distinct as enunciated in the previous Office Action.

The requirement is still deemed proper and is therefore made FINAL.

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Accordingly, claim 5 (non-elected species of Group I) and claims 8-41 (non-elected Groups II-XIV) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-4, 6 and 7 read on the elected species, SEQ ID NO: 1.

Upon consideration of the prior art, the search has been extended to include SEQ ID NO: 2-16.

Claims 1-4, 6 and 7 are currently being examined.

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

In the instant case, Applicant's abstract consists of two paragraphs. Appropriate correction is required.

4. The disclosure is objected to because of the following informality:

The disclosure on page 14 at lines 4-5 and on page 16 at lines 30-31 of the substitute specification filed 7/23/02 is incorrect with regard to the current address of ATCC. Please note the current address:

American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209

Appropriate correction is required.

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5. Claims 1-4, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the peptide recited in the instant claims.

The instant claims encompass: (1) a peptide *comprising* an HLA-binding peptide of human CD45 polypeptide *or a portion or variant of said peptide*, including wherein the peptide or the said portion or variant thereof is capable of binding to HLA-A0201 and eliciting a CTL response; (2) a peptide *comprising* at least one of SEQ ID NO: 1-16; or (3) a peptide according to "(1)" that forms a polypeptide fusion molecule which comprises an HLA heavy chain molecule joined via a flexible linker to an HLA-binding peptide of CD45 such that the HLA-binding peptide is able to occupy the peptide-binding groove of the HLA molecule. There is insufficient disclosure in the specification on such a peptide.

The specification discloses that "peptide of human CD45" polypeptide" is a peptide that has contiguous amino acid sequence of the CD45 polypeptide" and that the sequence of CD45 is given in the Leukocyte Antigen Fact Book, 2nd edition, page 244, 1997 (page 4 at lines 1-9). The specification further discloses that a "portion" is at least six consecutive amino acids of the given sequence such that the portion is still able to bind an HLA molecule in substantially the same way as a peptide consisting of the given amino acid sequence (page 5 at lines 25-30). The specification discloses that "variant" of a given amino acid sequence is that the side chains of some of the amino acid residues are altered such that the peptide is still able to bind to an HLA molecule in substantially the same way as a peptide consisting of the given amino acid sequence (page 6 at lines 1-20) and is still able to stimulate a CTL.

The art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, i.e., a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I

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molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with the class I molecule.

In addition, the art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr et al, Shastri et al, Bergmann et al, Wang et al, Perkins et al, Theobald et al and Gileadi et al) and that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neoepitopes can be created (Perkins et al) or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang et al).

The specification provides no description that the claimed peptide comprising (1) would bind to one the recited HLA molecule when present in a longer peptide of unknown length and flanked by amino acid sequences not present in the antigenic protein of origin and even more particularly when it is only a "portion" or a "variant" of an HLA-binding peptide of human CD45, (2) or would be recognized by CTL, i.e., there are no working examples of peptides comprising the recited SEQ ID NO or other peptides from human CD45 that are flanked by amino acid sequences not present in the contiguous sequence of human CD45, nor of "portions" or "variants".

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

6. Claims 1-4, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, (1) a peptide *comprising* an HLA-binding peptide of human CD45 polypeptide or a *portion or variant of said peptide*, including wherein the peptide or the said portion or variant thereof is capable of binding to HLA-A0201 and eliciting a CTL response; (2) a peptide *comprising* at least one of SEQ ID NO: 1-16; or (3) a peptide according to "(1)" that forms a polypeptide fusion molecule which comprises an HLA heavy chain molecule joined via a flexible linker to an HLA-binding peptide of CD45 such that the HLA-binding peptide is able to occupy the peptide-binding groove of the HLA molecule.

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The specification has not enabled the breadth of the claimed invention because the claims encompass: (1) a peptide *comprising* an HLA-binding peptide of human CD45 polypeptide *or a portion or variant of said peptide*, including wherein the peptide or the said portion or variant thereof is capable of binding to HLA-A0201 and eliciting a CTL response; i.e., the peptide comprises sequence other than that present in the contiguous sequence of the human CD45 polypeptide flanking the HLA-binding peptide or comprises a contiguous 6 amino acid stretch of an HLA-binding peptide from human CD45 that contains unrelated flanking sequence ("portion") or comprises a variant peptide that may be sequence unrelated to the primary sequence of human CD45; (2) a peptide *comprising* at least one of SEQ ID NO: 1-16, i.e., the peptide comprises sequence other than that present in the contiguous sequence of the human CD45 polypeptide flanking the HLA-binding peptide; or (3) a peptide according to "(1)" that forms a polypeptide fusion molecule which comprises an HLA heavy chain molecule joined via a flexible linker to an HLA-binding peptide of CD45 such that the HLA-binding peptide is able to occupy the peptide-binding groove of the HLA molecule, i.e., it is unpredictable that the peptide *comprising* an HLA-binding peptide of human CD45 polypeptide binds to the recited HLA molecule because it may contain flanking sequence that does not allow binding to occur. There is insufficient disclosure in the specification on such a peptide. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed peptide can be made and/or used.

The specification discloses that "peptide of human CD45" polypeptide" is a peptide that has contiguous amino acid sequence of the CD45 polypeptide" and that the sequence of CD45 is given in the Leukocyte Antigen Fact Book, 2nd edition, page 244, 1997 (page 4 at lines 1-9). The specification further discloses that a "portion" is at least six consecutive amino acids of the given sequence such that the portion is still able to bind an HLA molecule in substantially the same way as a peptide consisting of the given amino acid sequence (page 5 at lines 25-30). The specification discloses that "variant" of a given amino acid sequence is that the side chains of the amino acid residues are altered such that the peptide is still able to bind to an HLA molecule in substantially the same way as a peptide consisting of the given amino acid sequence (page 6 at lines 1-20) and is still able to stimulate a CTL.

As to the issue of "*comprises*", the specification does not disclose wherein there are flanking sequences that are not contiguous sequence of human CD45 polypeptide. There is no guarantee that said peptide would bind to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, i.e., a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A", "F") located at opposite ends of

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the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo, et al at page 366, column 1 lines 1-10.) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends" , but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27).

In addition, the art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr et al, Shastri et al, Bergmann et al, Wang et al, Perkins et al, Theobald et al and Gileadi et al) and that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neopeptides can be created (Perkins et al) or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang et al).

An undue amount of experimentation would be involved in determining longer peptides from the many possibilities that would be capable of binding to HLA and being recognized by CTL, and particularly when comprising a "portion" or "variant".

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-4 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is indefinite in the recitation of "said peptide" at line 2 because it is not clear what is meant, i.e., if the "said peptide" is "A peptide comprising" or "an HLA-binding peptide".

b. Claim 7 is indefinite in the recitation of "A peptide according to Claim 1 forming a polypeptide fusion molecule which comprises an HLA heavy chain molecule joined via a flexible linker to an HLA-binding peptide of CD45" because it is not clear what is meant, i.e., the claim appears to be drawn to a fusion protein comprising a peptide according to claim 1, and the peptide according to

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claim 1 comprises an HLA-binding peptide of CD45, not consisting of an HLA-binding peptide of CD45.

c. Claim 4 is indefinite in the recitation of "a polypeptide expressing the given amino acid sequence" because it is not clear what is meant. A "given amino acid sequence" is not recited in claim 4 nor in base claim 1.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-3 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by UniProt Accession No.Q29311 (1996) as evidenced by The Leukocyte Antigen Fact Book (IDS reference) and admissions in the specification at Example 1 and Figure 1.

UniProt Accession No.Q29311 teaches a 74 amino acid long polypeptide that is not the intact human CD45 polypeptide, said 74 amino acid long polypeptide comprises SEQ ID NO: 1 of the instant application, i.e., FLYDVIAST that is an HLA-A0201 binding peptide from human CD45.

Evidentiary reference The Leukocyte Antigen Fact Book teaches that CD45 protein(s) are found on all cells of hematopoietic origin, except erythrocytes, and further teaches the amino acid sequence of the human CD45 protein and that it is 1281 amino acid residues in length.

The admissions in the specification at Example 1 are that FLYDVIAST binds to HLA-A0201 and can generate peptide-specific allo-restricted CTL.

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11. Claims 1-3 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 92/13887 A1 as evidenced by The Leukocyte Antigen Fact Book (IDS reference) and admissions in the specification at Example 1 and Figure 1.

WO 92/13887 A1 teaches a 19-mer as well as a 20-mer peptide that comprises SEQ ID NO: 9 of the instant application, i.e., LILDVPPGV that is an HLA-A0201 binding peptide from human CD45. WO 92/13887 A1 further teaches a 19-mer as well as a 20-mer peptide that comprises SEQ ID NO: 10 of the instant application, i.e., TLILDVPPGV that is an HLA-A0201 binding peptide from human CD45 (page 11, peptide #3 from CD45). The peptides taught by WO 92/13887 A1 are not the intact human CD45 polypeptide.

Evidentiary reference The Leukocyte Antigen Fact Book teaches that CD45 protein(s) are found on all cells of hematopoietic origin, except erythrocytes, and further teaches the amino acid sequence of the human CD45 protein and that it is 1281 amino acid residues in length.

The admissions in the specification at Example 1 and Figure 1 are that LILDVPPGV and TLILDVPPGV bind to HLA-A0201.

12. Claims 1-3 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by UniProt Accession No. P06800 (1998) as evidenced by The Leukocyte Antigen Fact Book (IDS reference) and admissions in the specification at Example 1 and Figure 1.

UniProt Accession No. P06800 teaches a portion of the CD45 protein (amino acid residues 1-1152) that comprises SEQ ID NO: 12 of the instant application, i.e., ILPYDYNRV that is an HLA-A0201 binding peptide.

Evidentiary reference The Leukocyte Antigen Fact Book teaches that CD45 protein(s) are found on all cells of hematopoietic origin, except erythrocytes, and further teaches the amino acid sequence of the human CD45 protein and that it is 1281 amino acid residues in length.

The admissions in the specification at Example 1 and Figure 1 are that ILPYDYNRV binds to HLA-A0201.

13. Claims 1-3 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,060,054 as evidenced by The Leukocyte Antigen Fact Book (IDS reference) and admissions in the specification at Example 1 and Figure 1.

U.S. Patent No. 6,060,054 discloses a 553 amino acid residue long portion of human CD45 (SEQ ID NO: 13 amino acid residues 221-229) that comprises SEQ ID NO: 3 of the instant application, i.e., KLFTAKLNV that is a peptide that binds to HLA-A0201.

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Evidentiary reference The Leukocyte Antigen Fact Book teaches that CD45 protein(s) are found on all cells of hematopoietic origin, except erythrocytes, and further teaches the amino acid sequence of the human CD45 protein and that it is 1281 amino acid residues in length.

The admissions in the specification at Example 1 and Figure 1 are that KLFTAKLNV binds to HLA-A0201.

14. Claims 1-3 and 6 are rejected under 35 U.S.C. 102(a) as being anticipated by U.S. Patent No. 6,060,054 as evidenced by The Leukocyte Antigen Fact Book (IDS reference) and admissions in the specification at Example 1 and Figure 1.

U.S. Patent No. 6,060,054 discloses a 553 amino acid residue long portion of human CD45 (SEQ ID NO: 13 amino acid residues 221-229) that comprises SEQ ID NO: 3 of the instant application, i.e., KLFTAKLNV that is a peptide that binds to HLA-A0201.

Evidentiary reference The Leukocyte Antigen Fact Book teaches that CD45 protein(s) are found on all cells of hematopoietic origin, except erythrocytes, and further teaches the amino acid sequence of the human CD45 protein and that it is 1281 amino acid residues in length.

The admissions in the specification at Example 1 and Figure 1 are that KLFTAKLNV binds to HLA-A0201.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. Claims 1-4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/26328 A1 (IDS reference) in view of The Leukocyte Antigen Fact Book (2nd edition, pages 244-247, 1997, IDS reference) and Rammensee et al (MHC Ligands and Peptide Motifs, LANDES Bioscience, Springer, NY, 1997, pages 217-227 and 236-281).

WO 97/26328 A1 teaches a method of treating a disease, including leukemia, comprising administering allo-restricted allogeneic CTL specific for peptides from self proteins that are expressed in tumors and in a limited number of normal cells, tissue-specific differentiation antigens, and in the case of leukemia, CTL with specificity for leukemias can be generated against peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage and then used for adoptive immunotherapy of leukemia patients where they will

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eliminate leukemic cells and possibly some normal bone marrow derived cells. WO 97/26328 A1 teaches that possible loss of normal bone marrow cells is not expected to cause any problems because these patients are frequently treated with bone marrow transplantation from healthy donors (see entire article, especially page 19 at lines 21-30 and continuing onto page 20 at lines 1-5 and page 23 at lines 11-19). WO 97/26328 A1 further teaches that known CTL epitope peptides or newly identified peptides may be used, in the latter instance, the peptides that bind to a particular HLA class I molecule may be identified and may represent better targets for adoptive immunotherapy since they are likely to be subdominant peptides that are less likely to be immunoselected by the patient's CTL responses. WO 97/26328 A1 teaches methods for generating said CTL, and that the stimulator cell has a type of HLA class I molecule that is not present on the healthy individual's cells, and further teaches testing of binding to HLA class I molecules and for generating and stimulating CTL. WO 97/26328 A1 teaches that HLA-A0201 is particularly preferred allele that is present on the stimulator cells at a high frequency in the human population (page 27 at lines 19-30 and page 28 at line 1).

WO 97/26328 A1 does not teach the CD45 peptides recited in the instant claims 1-4 and 6, nor the CD45 peptide-HLA heavy chain fusion polypeptide recited in instant claim 7.

The Leukocyte Antigen Fact Book teaches that CD45 protein(s) are found on all cells of hematopoietic origin, except erythrocytes, and further teaches the amino acid sequence of the human CD45 protein and that it is 1281 amino acid residues in length.

Rammensee et al teach anchor residue motifs for peptides that bind to individual class I MHC molecules (HLA in humans) including HLA-A0201, and that most peptides that bind class I molecules are between 8 and 11 amino acid residues in length consonant with the length of peptide required to span the class I MHC binding groove. Rammensee et al teach methods of predicting MHC class I peptide epitopes using motifs to identify subsequences possessing the motif in proteins of interest. Rammensee et al teach that the motif for peptides that bind to HLA-A0201 is L or M at position 2 of the peptide and V or L at the carboxy-terminal position of the peptide, but that other endogenous peptides as well as CTL epitope peptides that bind to HLA-A0201 may have I, T, M or A at position 2 as well, and A, I, T, S or C at the carboxy-terminus. Rammensee et al teach that most peptides that bind to HLA-A0201 are 9 to 10 amino acid residues in length (pages 271-227 and 236-281).

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It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made peptides as per the teaching of Rammensee et al (see below) from the CD45 human protein taught by The Leukocyte Antigen Fact Book in the method taught by WO 97/26328 A1 for use in generating allo-restricted CTL with specificity for peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage and said allo-restricted CTL used for adoptive immunotherapy of leukemia patients.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 97/26328 A1 teaches that allo-restricted CTL that are specific for peptides that are expressed on leukemic cells but not in cells outside the hematopoietic lineage are useful to treat patients with leukemia and that such a use is not expected to cause any problems due to possible loss of normal bone marrow cells because these patients are frequently treated with bone marrow transplantation from healthy donors, and The Leukocyte Antigen Fact Book teaches that the human CD45 protein is found on all cells of hematopoietic origin.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of epitope prediction taught by Rammensee et al using the peptide binding motif of a frequently expressed HLA molecule such as HLA-A0201 to scan the human CD45 protein sequence taught by The Leukocyte Antigen Fact Book for subsequences that would potentially bind to HLA-A0201 and function to stimulate CTL as taught by Rammensee et al and by WO 97/26328 A1, in effect to generate peptides of 9 or 10 amino acid residues in length that would be predicted to bind to HLA-A0201 from the sequence of human CD45 protein, said peptides having the motif anchor residues at positions 2 and 9 or 10, and to have produced the peptides recited in the instant claims consisting of SEQ ID NO: 1-5, 7-13, 15 and 16 which are subsequences of human CD45 that have the anchor residues taught by Rammensee et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to generate peptides as per the teaching of Rammensee et al using the human CD45 protein sequence taught by The Leukocyte Antigen Fact Book to use in the method taught by WO 97/26328 A1 of identifying peptides that can bind to alleles present in high frequency in the population such as HLA-A0201 for generation of allo-restricted CTL that are useful in treating leukemia patients.

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17. Claims 1-4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/26328 A1 (IDS reference) in view of The Leukocyte Antigen Fact Book (2nd edition, pages 244-247, 1997, IDS reference), LANDES Bioscience, Springer, NY, 1997, pages 217-227 and 236-281) and U.S. Patent No. 6,602,510 B1.

WO 97/26328 A1 teaches a method of treating a disease, including leukemia, comprising administering allo-restricted allogeneic CTL specific for peptides from self proteins that are expressed in tumors and in a limited number of normal cells, tissue-specific differentiation antigens, and in the case of leukemia, CTL with specificity for leukemias can be generated against peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage and then used for adoptive immunotherapy of leukemia patients where they will eliminate leukemic cells and possibly some normal bone marrow derived cells. WO 97/26328 A1 teaches that possible loss of normal bone marrow cells is not expected to cause any problems because these patients are frequently treated with bone marrow transplantation from healthy donors (see entire article, especially page 19 at lines 21-30 and continuing onto page 20 at lines 1-5 and page 23 at lines 11-19). WO 97/26328 A1 further teaches that known CTL epitope peptides or newly identified peptides may be used, in the latter instance, the peptides that bind to a particular HLA class I molecule may be identified and may represent better targets for adoptive immunotherapy since they are likely to be subdominant peptides that are less likely to be immunoselected by the patient's CTL responses. WO 97/26328 A1 teaches methods for generating said CTL, and that the stimulator cell has a type of HLA class I molecule that is not present on the healthy individual's cells, and further teaches testing of binding to HLA class I molecules and for generating and stimulating CTL. WO 97/26328 A1 teaches that HLA-A0201 is particularly preferred allele that is present on the stimulator cells at a high frequency in the human population (page 27 at lines 19-30 and page 28 at line 1).

WO 97/26328 A1 does not teach the CD45 peptides recited in the instant claims 1-4 and 6, nor the CD45 peptide-HLA heavy chain fusion polypeptide recited in instant claim 7.

The Leukocyte Antigen Fact Book teaches that CD45 protein(s) are found on all cells of hematopoietic origin, except erythrocytes, and further teaches the amino acid sequence of the human CD45 protein and that it is 1281 amino acid residues in length.

U.S. Patent No. 6,602,510 B1 discloses that peptides that bind to HLA class I molecules are about 8 to about 13 amino acid residues in length and possess amino acid residues at certain positions in the peptide sequence that are required for allele-specific binding. U.S. Patent No. 6,602,510 B1 discloses that a supertype motif is a peptide binding specificity shared by HLA molecules

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encoded by two or more HLA alleles, and that vaccines which bind to HLA supertypes such as A2, A3 and B7 will afford broad, non-ethnically biased population coverage. U.S. Patent No. 6,602,510 B1 discloses that the HLA-A2 supermotif is L, I, V, M, A, T or Q at position 2 of the peptide, and I, V, M, A, T or L at the carboxy-terminus of the peptide. U.S. Patent No. 6,602,510 B1 discloses that 9-mer subsequences of tumor-associated antigenic proteins were scanned to identify potential HLA-A2 supertype allele binding peptides, i.e., that would bind to HLA-A0201 as well as other alleles in the supertype (especially column 18 at lines 34, column 2 at lines 58-column 3 at lines 1-3, column 13 at lines 11-15, Table 2 and 2A, Table 4).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the peptides as per the disclosure of U.S. Patent No. 6,602,510 B1 (see below) from the CD45 human protein taught by The Leukocyte Antigen Fact Book for use in the method taught by WO 97/26328 A1 for generating allo-restricted CTL with specificity for peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage and said allo-restricted CTL used for adoptive immunotherapy of leukemia patients.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 97/26328 A1 teaches that allo-restricted CTL that are specific for peptides that are expressed on leukemic cells but not in cells outside the hematopoietic lineage are useful to treat patients with leukemia and that such a use is not expected to cause any problems due to possible loss of normal bone marrow cells because these patients are frequently treated with bone marrow transplantation from healthy donors, and The Leukocyte Antigen Fact Book teaches that the human CD45 protein is found on all cells of hematopoietic origin,.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of epitope prediction disclosed by U.S. Patent No. 6,602,510 B1 using the peptide binding motif of a frequently expressed HLA molecule such as HLA-A0201 to scan the human CD45 protein sequence taught by The Leukocyte Antigen Fact Book for subsequences that would potentially bind to HLA-A0201 and function to stimulate CTL as disclosed by U.S. Patent No. 6,602,510 B1 and as taught by WO 97/26328 A1, in effect to generate peptides of 9 or 10 amino acid residues in length that would be predicted to bind to HLA-A0201 from the sequence of human CD45 protein, said peptides having the motif anchor residues at positions 2 and 9 or 10, and to have produced the peptides recited in the instant claims consisting of SEQ ID NO: 1-5 and 7- 16 which are subsequences of human CD45 that have the anchor residues disclosed by U.S. Patent No. 6,602,510 B1.

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One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to generate peptides as per the disclosure of U.S. Patent No. 6,602,510 B1 using the human CD45 protein sequence taught by The Leukocyte Antigen Fact Book to use in the method taught by WO 97/26328 A1 of identifying peptides that can bind to alleles present in high frequency in the population such as HLA-A0201 for generation of allo-restricted CTL that are useful in treating leukemia patients.

18. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/26328 A1 (IDS reference) in view of The Leukocyte Antigen Fact Book (2nd edition, pages 244-247, 1997, IDS reference) and Rammensee et al (MHC Ligands and Peptide Motifs, LANDES Bioscience, Springer, NY, 1997, pages 217-227 and 236-281) as applied to claims 1-4 and 6 above, and further in view of Mottez et al (J. Exp. Med. 181: 1995, pages 493-502).

WO 97/26328 A1, The Leukocyte Antigen Fact Book (2nd edition, pages 244-247, 1997, IDS reference) and Rammensee et al have been discussed above, hereafter referred to as "the combined references".

The combined references do not teach the fusion polypeptide recited in instant claim 7 comprising an HLA heavy chain molecule joined via a flexible linker to an HLA-binding peptide of CD45.

Mottez et al teach fusion polypeptides comprising MHC class I heavy chain fused to a spacer molecule and a peptide. The spacer molecules taught by Mottez et al are poly-glycine spacers or spacers additionally containing a proline and a serine. Mottez et al teach that the peptide is able to occupy the peptide-binding groove of the class I molecule, and that such constructs can be recognized by CTL specific for the peptide/MHC class I combination, and that the availability of MHC class I molecules bound to a single peptide provides valuable tools for the manipulation of CTL responses. Mottez et al teach that use of such constructs can produce cell lines in which the density of the chosen MHC-peptide complex would be considerably increased, and that such fusions may prove useful for manipulating the immune response, in particular when the antigenic peptide has a low affinity for the MHC molecule (see entire article, especially abstract, introduction, materials and methods, Table 1 and discussion sections).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made fusion polypeptides taught by Mottez et al using HLA-A0201 and the peptides identified in the method of the invention of the combined references, i.e., HLA-A0201 linked via a spacer molecule to a CD45 peptide.

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One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more effectively generate all-specific CTL as per the teaching of the combined references because the combined references teach the identification of potential HLA-A0201 binding peptides from human CD45 and generation of all-restricted CTL using those peptides and Mottez et al teach fusion polypeptides comprising MHC class I heavy chain fused to a spacer molecule and a peptide are superior in that they present peptide/MHC complexes at a higher density and are useful for manipulating the immune response and in particular, when peptides are not high affinity binding peptides.

With regard to the limitation "a flexible linker", Mottez et al teach poly-glycine linkers, so it is an expected property that the said linkers are flexible because glycine is the smallest amino acid residue with no side chains and maximum rotational movement about the peptide bond axis.

19. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/26328 A1 (IDS reference) in view of The Leukocyte Antigen Fact Book (2nd edition, pages 244-247, 1997, IDS reference) and U.S. Patent No. 6,602,510 B1 as applied to claims 1-4 and 6 above, and further in view of Mottez et al (J. Exp. Med. 181: 1995, pages 493-502).

WO 97/26328 A1, The Leukocyte Antigen Fact Book (2nd edition, pages 244-247, 1997, IDS reference) and U.S. Patent No. 6,602,510 B1 have been discussed above, hereafter referred to as "the combined references".

The combined references do not teach the fusion polypeptide recited in instant claim 7 comprising an HLA heavy chain molecule joined via a flexible linker to an HLA-binding peptide of CD45.

Mottez et al teach fusion polypeptides comprising MHC class I heavy chain fused to a spacer molecule and a peptide. The spacer molecules taught by Mottez et al are poly-glycine spacers or spacers additionally containing a proline and a serine. Mottez et al teach that the peptide is able to occupy the peptide-binding groove of the class I molecule, and that such constructs can be recognized by CTL specific for the peptide/MHC class I combination, and that the availability of MHC class I molecules bound to a single peptide provides valuable tools for the manipulation of CTL responses. Mottez et al teach that use of such constructs can produce cell lines in which the density of the chosen MHC-peptide complex would be considerably increased, and that such fusions may prove useful for manipulating the immune response, in particular when the antigenic peptide has a low affinity for the MHC molecule (see entire article, especially abstract, introduction, materials and methods, Table 1 and discussion sections).

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It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made fusion polypeptides taught by Mottez et al using HLA-A0201 and the peptides identified in the method of the invention of the combined references, i.e., HLA-A0201 linked via a spacer molecule to a CD45 peptide.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more effectively generate all-specific CTL as per the teaching of the combined references because the combined references teach the identification of potential HLA-A0201 binding peptides from human CD45 and generation of all-restricted CTL using those peptides and Mottez et al teach fusion polypeptides comprising MHC class I heavy chain fused to a spacer molecule and a peptide are superior in that they present peptide/MHC complexes at a higher density and are useful for manipulating the immune response and in particular, when peptides are not high affinity binding peptides.

With regard to the limitation "a flexible linker", Mottez et al teach poly-glycine linkers, so it is an expected property that the said linkers are flexible because glycine is the smallest amino acid residue with no side chains and maximum rotational movement about the peptide bond axis.

20. SEQ ID NO: 6 appears to be free of the art.

21. No claim is allowed.

22. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

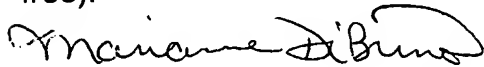
23. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
May 5, 2005



CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600